



Mefloquine Use and Hospitalizations Among U.S. Service Members, 2002-2004

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Background

- ◆ Malaria infects an estimated 500 million people and causes between 1-3 million deaths annually
- ◆ Few mosquito-borne diseases have inflicted greater disease burden upon US deployed forces
 - Guadalcanal - 1943
 - Liberia - 2003
- ◆ In 1989, FDA approved mefloquine (Lariam) for malaria chemoprophylaxis



Background

- ◆ Although mefloquine is highly effective at preventing malaria, studies have associated its use with adverse events
 - Danish travelers taking mefloquine reported elevated risk for depression, strange thoughts, and altered spatial perception when compared to chloroquine-proguanil users (Petersen et al., 2000)
 - Nested case control study of UK citizens using electronic prescription and outcome data identified positive associations among mefloquine-prescribed individuals for psychosis and panic attacks compared to past users of other antimalarials (Meier et al., 2004)
- ◆ Although mefloquine is generally considered well-tolerated in **military** populations, previous studies have produced mixed results



Studies in Military Populations

- ◆ Randomized controlled trials
 - Indonesian soldiers at increased risk for reporting neurological symptoms, headache, or dizziness when randomized to mefloquine rather than doxycycline (Ohrt et al., 1997)
 - US service members taking mefloquine reported significantly more insomnia or nightmares compared to those taking doxycycline (Wallace et al., 1996)
 - US Marines randomized to mefloquine reported more depressive feelings, sleep disturbances, and increased dream activity compared to those taking chloroquine (Boudreau et al., 1993)



Studies in Military Populations

- ◆ Observational studies have reported mefloquine is generally safe and effective for use in military populations
 - In study of Dutch Marines, no observed relationship between serum mefloquine concentrations and incidence of adverse events (Jaspers et al., 1996)
 - Incidence of side effects among UK military personnel taking mefloquine not significantly different from those taking chloroquine-proguanil (Croft et al., 1997)
 - Among Australian soldiers in East Timor, 6.5% withdrew from mefloquine use due to adverse events. However, 94% of those who remained on mefloquine stated they would use it again on future deployments, compared to 89% of those who took doxycycline. (Kitchener et al., 2005)



Study Objectives

- ◆ To describe morbidity potentially associated with mefloquine use, as measured by objective, electronic data on prescriptions and hospitalizations
- ◆ To provide a foundation for further antimalarial research efforts with US military populations



Study Population

- ◆ All US service members who were on active duty during the period January 1, 2002 through December 31, 2002
- ◆ No antimalarial prescription between October 1, 2001 and December 31, 2001
- ◆ Mefloquine-prescribed group
 - To minimize exposure misclassification, individual must be prescribed at least 7 mefloquine tablets per prescription
 - Service members must be identified as deployed and deployment must overlap time period for mefloquine prescription



Study Population

- ◆ Two reference groups:

Europe/Japan group

Includes service members with active duty zip codes for either Europe or Japan during 2002, with no evidence of having been deployed nor having received a prescription for mefloquine, or chloroquine, or more than 14 tablets of doxycycline during the observation period

Other Deployed group

Includes service members identified as having started deployment in
2002 but not having received a prescription for mefloquine, or chloroquine, or more than 14 tablets of doxycycline while deployed



Data Sources: Independent Variables

- ◆ Deployment status determined from DMDC pay files as having received combat zone tax exclusion or imminent danger pay
- ◆ Mefloquine prescriptions
 - Obtained from Military Health System, Management Analysis & Reporting Tool (M2), Pharmacy Data Transaction Service
 - If more than one qualifying prescription-deployment combination, first occasion chosen as the exposure event



Data Sources: Hospitalizations

- ◆ Link cohort to Standard Inpatient Data Record and Health Care Service Record databases to obtain hospitalization data
- ◆ ICD-9-CM Diagnosis Codes:
 - Any cause hospitalization, excluding pregnancy, childbirth, & associated complications
 - Hospitalizations among 14 ICD-9-CM categories
 - Mental disorders stratified into 5 primary categories
 - Hospitalizations of interest to Naval Medical Center San Diego study



Statistical Analysis

- ◆ Descriptive analyses
- ◆ Cox proportional hazards time-to-event modeling with adjustment for:
 - Age
 - Sex
 - Military rank
 - Service branch
 - Race/ethnicity
 - Marital status
 - Prior hospitalizations for any cause
 - Occupation (combat/other)



Follow-up Period

| Group | Follow-up Began When: | Follow-up Ended When First of Either: |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mefloquine-prescribed | Upon return from deployment following first mefloquine/deployment combination | 1. Complete 12 months follow-up 2. Separate from service 3. Begin new deployment 4. New anti-malarial prescription 5. Hospitalization of interest 6. March 31, 2004 |
| Other deployed | Upon return from deployment following first qualifying deployment | |
| Europe/Japan | January 1, 2002 for those with Europe/Japan duty zip on this date, or first day of first month in 2002 in which duty zip was Europe/Japan | In addition to above: 7. When duty zip no longer equaled Europe/Japan |

NOTE: Must have been followed for a minimum of 2 months to participate in the study



Results

Demographic Characteristics of Mefloquine-Prescribed, US Military Residing in Europe/Japan, or Deployed, 2002-2004

| | Mefloquine (%) <i>n</i> =8,858 | Europe/Japan (%) <i>n</i> =156,203 | Other Deployed (%) <i>n</i> =232,381 |
|-----------------------|--------------------------------------|------------------------------------------|-----------------------------------------------|
| Sex | | | |
| Male | 93.1 | 82.6 | 89.7 |
| Female | 6.9 | 17.4 | 10.3 |
| Age | | | |
| 17-24 | 51.0 | 46.8 | 47.2 |
| 25-34 | 33.2 | 33.0 | 32.0 |
| ≥ 35 | 15.8 | 20.2 | 20.8 |
| Race/Ethnicity | | | |
| White, non-Hispanic | 68.7 | 60.0 | 65.9 |
| Black, non-Hispanic | 16.7 | 23.0 | 18.6 |
| Hispanic | 9.6 | 9.8 | 9.3 |
| Other | 5.0 | 7.2 | 6.2 |
| Marital Status | | | |
| Single | 71.8 | 68.0 | 67.6 |
| Married | 28.2 | 32.0 | 32.4 |

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|-------------------------------|--------------------------------------|------------------------------------------|-----------------------------------------------|
| Service | | | |
| Army | 79.3 | 39.9 | 25.4 |
| Air Force | 18.8 | 24.7 | 28.7 |
| Marine Corps | 1.1 | 11.8 | 9.9 |
| Navy | 0.8 | 23.6 | 35.9 |
| Rank | | | |
| Enlisted | 90.7 | 92.4 | 88.8 |
| Officer | 9.3 | 7.6 | 11.2 |
| Occupational Category | | | |
| Infantry, gun crews, seamen | 37.1 | 15.8 | 26.2 |
| Electrical repair | 7.0 | 10.1 | 10.2 |
| Mechanical equipment repair | 9.2 | 17.6 | 22.1 |
| Functional support and admin | 12.9 | 19.2 | 13.0 |
| Service and supply | 10.4 | 10.9 | 8.1 |
| Communication/intelligence | 9.7 | 8.9 | 9.6 |
| Healthcare | 4.7 | 7.8 | 3.3 |
| Construction | 2.6 | 4.2 | 3.6 |
| Other technical and specialty | 4.0 | 2.8 | 2.8 |
| Other | 2.4 | 2.7 | 1.1 |

Results of Cox Proportional Hazards Analysis for Hospitalizations Among U.S. Service Members Prescribed Mefloquine, 2002-2004

| Category (ICD-9-CM codes) | Europe/Japan | | Other Deployed | |
|---------------------------------------------|--------------|-------------------|----------------|--------|
| | HR | 95% CI | HR | 95% CI |
| Any cause (excluding: 630-677) | 0.4 | 0.39, 0.57 | 0.9 | 0.79, |
| Infectious/parasitic (001-139) | 7 | 0.57, 1.94 | 4 | 1.12 |
| | 1.0 | | 1.0 | 0.59, |
| | 6 | | 8 | 1.99 |
| Neoplasms (140-239) | 0.9 | 0.37, 2.21 | 1.1 | 0.46, |
| | 0 | | 3 | 2.77 |
| Endocrine, nutritional, metabolic (240-279) | 1.0 | 0.59, 1.82 | 1.3 | 0.77, |
| | 4 | | 4 | 2.35 |
| Blood & Blood Forming Organs (280-289) | 0.5 | 0.19, 1.36 | 0.6 | 0.24, |
| | 1 | | 5 | 1.74 |
| Mental disorders (290-319) | 0.7 | 0.55, 1.07 | 1.2 | 0.87, |
| | 6 | | 3 | 1.72 |
| Nervous system (320-389) | 0.5 | 0.26, 1.32 | 0.7 | 0.34, |
| | 8 | | 6 | 1.73 |
| Circulatory system (390-459) | 0.6 | 0.31, 1.18 | 0.6 | 0.35, |
| | 1 | | 9 | 1.34 |
| Respiratory system (460-519) | 0.4 | 0.23, 0.86 | 0.8 | 0.42, |
| | 4 | | 1 | 1.58 |
| Digestive system (520-579) | 0.5 | 0.34, 0.79 | 0.9 | 0.60, |
| | 2 | | 0 | 1.37 |
| Genitourinary system (580-629) | 0.7 | 0.40, 1.36 | 1.1 | 0.67, |

Results of Cox Proportional Hazards Analysis for Hospitalizations Among U.S. Service Members Prescribed Mefloquine, Specific Psychological Conditions and Other Diagnoses, 2002-2004

| Category (ICD-9-CM codes) | Europe/Japan | | Other Deployed | |
|--------------------------------|--------------|-------------------|----------------|-------------|
| | HR | 95% CI | HR | 95% CI |
| Somatoform disorders | -- | -- | -- | -- |
| Mood disorders | 0.37 | 0.15, 0.90 | 0.50 | 0.21, 1.22 |
| Anxiety disorders | 0.92 | 0.40, 2.10 | 1.27 | 0.55, 2.91 |
| Post-traumatic stress disorder | 0.79 | 0.11, 5.91 | 1.66 | 0.21, 12.85 |
| Mixed syndromes | 0.91 | 0.33, 2.51 | 0.99 | 0.36, 2.73 |
| Substance use disorders | 0.72 | 0.45, 1.15 | 1.20 | 0.75, 1.90 |
| Other disorders | 0.71 | 0.45, 1.13 | 1.54 | 0.96, 2.46 |
| Personality disorders | 0.46 | 0.21, 1.05 | 1.39 | 0.60, 3.20 |
| Adjustment reaction | 0.78 | 0.45, 1.38 | 1.68 | 0.95, 2.97 |
| Nystagmus | -- | -- | -- | -- |
| Vertiginous syndromes | 3.17 | 0.32, 31.18 | 5.53 | 0.59, 52.06 |
| Dizziness and giddiness | -- | -- | -- | -- |



Discussion

When compared to the **Europe/Japan** reference group...

- ◆ Mefloquine-prescribed group was at significantly lower risk for
 - Any cause hospitalization
 - Diseases of the respiratory, digestive, or musculoskeletal system
 - Ill-defined conditions and Injuries & poisonings
 - Mood disorders

- ◆ Findings may reflect
 - Selection bias as a result of selecting those most fit to deploy
 - Medical encounter reporting differences between Europe/Japan and US
 - Artifact of multiple comparisons



Discussion

When compared to the **other deployed** reference group...

- ◆ No statistically significant differences were noted
- ◆ Findings may reflect :
 - Mefloquine is unlikely to be associated with hospitalizations over a broad range of outcomes
 - The mefloquine-prescribed group has a greater proportion of individuals in combat occupations (37.1% vs. 26.1%), and deployed to Afghanistan (70% vs. 4.2%). Unequal participation in potentially hazardous missions may confound mental health analyses



Discussion - Limitations

- ◆ Use of prescription database as surrogate for mefloquine exposure
 - Potentially reduced sensitivity among mefloquine-prescribed group since not known whether service members actually took medication they were prescribed
 - Among other deployed reference group, may be reduced specificity in mefloquine exposure assessment, as a small percentage of individuals in reference group may have used mefloquine while deployed
- ◆ Using inpatient hospitalization data restricts analyses to medical conditions of severity sufficient to warrant hospitalization
- ◆ Large number of analyses increases likelihood of finding a statistically significant association



Discussion - Strengths

- ◆ Size of mefloquine-prescribed group, as well as reference groups, allowed ample power to explore associations, with the exception of very rare outcomes.
- ◆ Use of 2 “healthy” reference groups allowed comparisons to be made with another population with good specificity for mefloquine exposure (Europe/Japan reference group), and one population that was more homogeneous to mefloquine exposed group (other deployed reference group).
- ◆ Use of objective data eliminates possibility of recall bias.



Conclusion

- ◆ Overall, mefloquine-prescribed active duty service members were not at increased risk for hospitalizations over a broad range of outcomes.

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